

Palladium-103: A New Radioactive Source in the Treatment of Unresectable Carcinoma of the Pancreas: A Phase I-II Study

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Palladium-103 (Pd-103) is introduced in brachytherapy procedures because of its favorable physical properties, including its low energy, rapid dose fall-off, short half-life, and total cumulative dose delivery at a higher dose rate than iodine-125 (I-125) isotope. Intraoperative brachytherapy using I-125 pellets was reported to provide significant palliation and meaningful prolongation of life in highly selected patients with unresectable carcinoma of the pancreas. After considering some of the advantages of Pd-103 over I-125, we designed a phase I-II clinical trial to assess the feasibility of intraoperative Pd-103 in unresectable carcinoma of the pancreas to study the related morbidity when combined with chemotherapy and external beam radiation, and to evaluate the impact on palliation and local control rates. Between December 1989 and December 1993, 15 patients with biopsy-proven unresectable adenocarcinoma of the pancreas were treated with interstitial Pd-103 implants during laparotomy. In 13 patients the lesion was located in the head of the pancreas, in one patient in the uncinate process, and in one patient in the body of the pancreas. The stage distribution was as follows: T1 = 2; T2 = 6, and T3 = 7. In addition, all patients underwent biliary and gastric bypass. The mean number of Pd-103 pellets was 45; the mean total activity to obtain a matched peripheral dose (MPD) of 11,000 cGy was 68.9 mCi. The mean tumor volume encompassing the MPD was 16.5 cc. All patients received postoperative external beam radiation (4,500 cGy over 4½ weeks) and chemotherapy (5-fluorouracil and mitomycin C). This combined treatment, consisting of intraoperative brachytherapy using Pd-103 and postoperative external beam radiation with chemotherapy, was well tolerated in all patients. There were no treatment-related mortalities, and no serious complications, such as bleeding or fistula formation. Pain relief was obtained within 3–6 weeks in 10 out of 12 patients presenting with pain. Survival ranged from 6 to 24 months (median 10 months). The study suggests that Pd-103 can be considered an alternative to I-125 for interstitial brachytherapy for unresectable carcinoma of the pancreas. Symptom relief appeared to occur faster and complications are significantly less. However, this study did

Accepted for publication October 31, 1995.

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not show any improvement in the median survival rate over I-125 due to the advanced stage cancer in the majority of patients in the study.

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KEY WORDS: pancreatic carcinoma, Palladium-103, brachytherapy, external beam radiation, chemotherapy

INTRODUCTION

Despite advances in surgery and radiotherapy with or without chemotherapy, the prognosis for carcinoma of the pancreas continues to be poor, with greater than 90% of patients succumbing to disease [1–8]. Less than 20% of newly diagnosed patients are potential candidates for surgical resection with curative intent [1]. Many reports have indicated that failure to control disease may have contributed to the ultimate death of the patients [1,2,5,9]. External beam radiation alone, or in combination with chemotherapy, failed to show meaningful improvement in outcome. Combination chemotherapy with external radiation was reported to show modest improvement in median survival over external beam radiation alone [7,9]. Intraoperative implantation of I-125 radioactive sources has been attempted in patients with locally advanced carcinoma of the pancreas, but the overall results were not significantly different [7]. A small subgroup of patients in that series who received postoperative chemotherapy in addition to brachytherapy showed a significant improvement in median survival (18.5 months).

One disadvantage of the use of I-125 is its long half-life and the resultant low dose rate at which the radiation is delivered. Palladium-103 appears to have some theoretical advantages over I-125; its shorter half-life (17 days) permits the implementation of higher total activities, which in the short term results in increased dose rates for a given total dose [10,11]. At the same time, the energy spectrum of the gamma rays for Pd-103, which is similar to that of I-125 [20–35 keV vs. 27–35 keV], preserves the advantage of the sparing effects to the surrounding tissues, such as the stomach, small bowel, and anastomosis sites. This phase I-II study has been undertaken to study the feasibility, toxicity, and effective palliation using Pd-103 in the intraoperative brachytherapy of unresectable, localized adenocarcinoma of the pancreas.

MATERIALS AND METHODS

From January 1989 through April 1993, 15 patients with biopsy-proven unresectable carcinoma of the pancreas underwent permanent palladium-103 implantation followed by chemotherapy and external beam irradiation. The candidates for implantation were patients in whom a computed tomography (CT) scan confirmed the presence of a tumor without evidence of metastases and patients found during laparotomy to have unresectable tu-

mors because of local extension to major vascular structures or lymph node involvement.

The mean age of the whole group was 66.1 years. Patients were staged according to the American Joint Committee (AJC) staging classification. Pain was the presenting symptom in 12 of 15 (80%) patients. Thirteen patients had tumors located in the head of the pancreas, one patient in the uncinate process, and one patient in the body. Careful evaluation of the tumor volume was performed; the liver, celiac, and portal nodes, and the abdominal cavity were examined for metastases and were biopsied. All patients underwent biliary and gastric bypass. The total activity and number of seeds to be implanted was based on the Anderson nomogram [12]. The average dimensions of the tumor, as measured in the X, Y, and Z directions with a caliper, were evaluated and recorded in order to determine the required total activity.

The seeds were placed approximately 0.5–1.0 cm from the surface of the pancreas in order to avoid radiation damage to the stomach and duodenum (Fig. 1). A segment of omentum was placed over the implanted tumor to increase the distance between the implanted seeds and adjacent viscera. Small surgical hemoclips were placed on the anterior surface of the tumor to determine the target volume for dosimetry. A mean number of 45 Pd-103 pellets (range 11–80) was implanted in each of the 15 cases. The mean total activity to obtain a MPD of

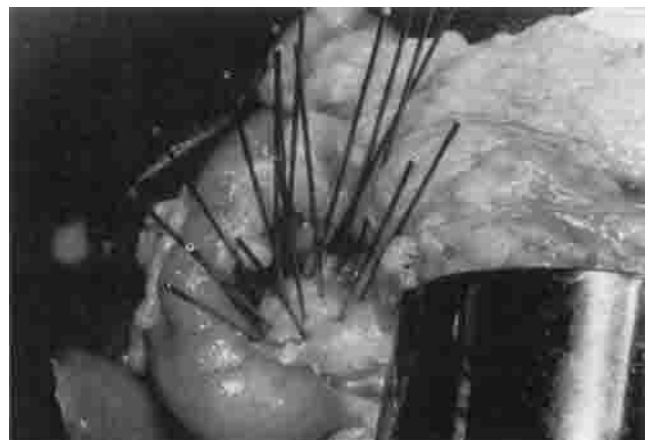


Fig. 1. Shows intraoperative afterloading needle placement into the head of pancreas. Also the C loop of the duodenum is shown. The needles are afterloaded with radioactive Pd-103 sources.



Fig. 2. Radiograph showing Pd-103 seed distribution and dose distribution for an unresectable lesion in the body of the pancreas.

11,000 cGy was 68.9 mCi. A MPD isodose curve of 11,000 cGy using Pd-103 seeds encompassed a mean tumor volume of 19.5 cc. Postoperative stereo shift localization films were performed in order to determine the position of each seed in the implanted tumor volume. The relationships between the treated volume and the anatomical landmarks were demonstrated by generating an anterior-posterior and a lateral centroid plane dose distribution that was superimposed on the corresponding radiographs (Fig. 2). An isometric view of the dose distribution was also obtained.

Follow-up films were performed at 2 weeks after the procedure. All patients received postoperative external beam radiation therapy (4,500 cGy in 4½ weeks) and one course of chemotherapy (mitomycin and fluoruracil) administered over 24 hours for 5 days (Fig. 3). No maintenance chemotherapy was given.

RESULTS

Figure 4 shows the overall survival of the entire group. The median survival for this group was 10 months. Two patients with early stage disease (T1N0) survived for 18 and 24 months. Pain relief was the most significant subjective response affected by the implant. Significant pain relief was observed in 10 of 12 patients presenting with pain (88%). Follow-up films performed to assess tumor response showed a 30% tumor regression in almost half of all patients (Fig. 5). There were 10 patients who had CT scans to assess tumor response 6 months after the procedure, and 8 (80%) had no tumor progression.

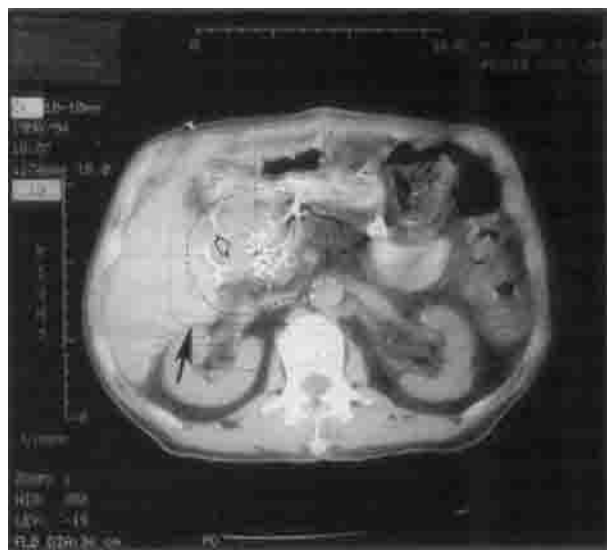


Fig. 3. A CT scan of the abdomen showing a composite dose distribution with Pd-103 brachytherapy and 4,500 cGy external beam radiation delivering a cumulated dose of 8,000 cGy isodose line. (The closed arrow indicates the isodose.) Normal structures, such as the spinal cord, kidneys, liver, stomach, etc., receive a significantly less dose of radiation. The open arrow shows the location of the duodenum.

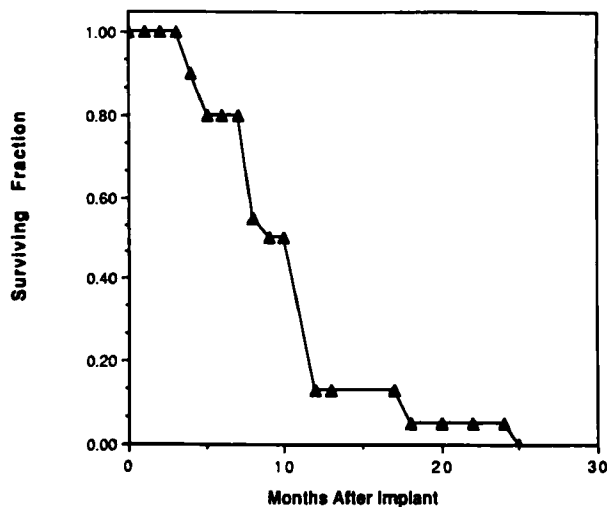


Fig. 4. Disease-related actuarial survival curve following intraoperative brachytherapy.

There was no evidence of postimplantation bleeding, sepsis, cyst, and fistula formulation. One patient experienced prolonged diarrhea after a Pd-103 implant that was treated conservatively. Most patients developed transient nausea and oral mucositis after external beam radiation and chemotherapy administration, which was managed with conservative treatment.

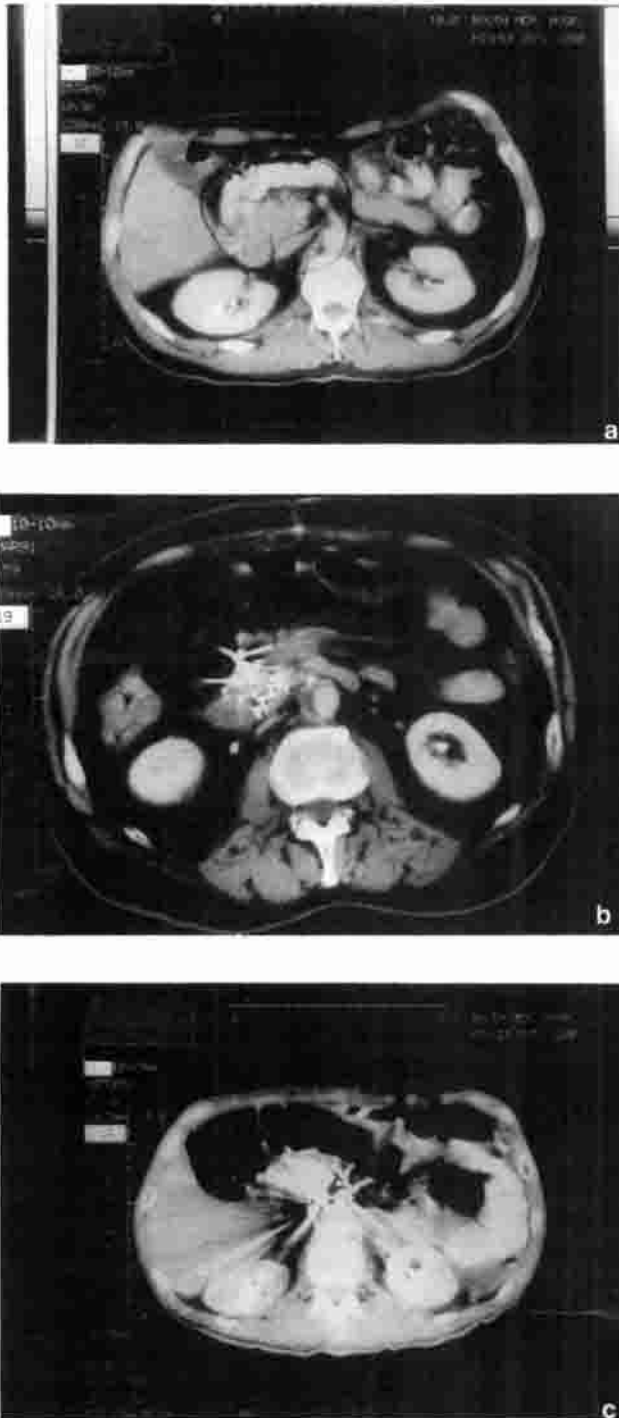


Fig. 5. **a:** CT scan of the abdomen showing a pancreatic head lesion in a 51-year-old patient. **b:** CT scan of the abdomen of the same patient showing Pd-103 radioactive sources uniformly distributed in the head of the pancreas, sparing the duodenum. **c:** At the 24-month follow-up, a CT scan of the abdomen is shown with no progression of local disease. The patient died of distant metastases in the lung and neck.

DISCUSSION

From our experience and the accumulated experience of other institutions, it is suggested that I-125 implantation

of unresectable pancreatic tumors offers high control of the primary tumor and significant palliation of symptoms [7]. The data also suggest that local control rates can be enhanced by the addition of chemotherapy [7]. In our previous series we reported on I-125 implantation in pancreatic carcinoma [7]. Ninety-eight patients with biopsy-proven unresectable adenocarcinoma of the pancreas were implanted; median survival for the whole group was 7 months. Ten T1N0M0 patients who received adjuvant chemotherapy survived for a median of 18.9 months. Pain relief was noted in 37 of 57 patients. However, the long half-life time of I-125 and the resultant very low dose rate at which the radiation is administered were considered as unfavorable for tumors with short doubling times. To address this issue, we designed a phase I-II study to assess the related morbidity of Pd-103 when combined with chemotherapy and external beam radiation, and to evaluate the impact on palliation and local control rates. Palladium-103 has similar photon characteristics, rapid dose fall-off, short half life, and a total cumulative dose that can be delivered at a higher dose rate than I-125. These properties make it more favorable for the treatment of rapidly growing tumors such as pancreatic carcinoma, because most of the dose and radiation is delivered over a short period (8 weeks) and prolonged radiation exposure of the adjacent normal tissue is minimized.

Our data indicate that when a group of nonselected patients with localized unresectable carcinoma of the pancreas was treated with permanent Pd-103 seed implants, the overall median survival (10 months) was not significantly different from that observed in the literature for similar patients treated with other modalities [5,6,13,14]. All patients succumbed to distant metastases. In our previous series of 98 patients treated with an intraoperative I-125 implant, we reported an overall median survival rate of 7 months, with a small subgroup of patients with early stage disease (T1N0) who survived for 18.5 months [7]. In our present series, two patients with T1N0 disease survived for 18 and 24 months.

Shipely et al. reported the Massachusetts General Hospital experience of 12 patients with locally unresectable pancreatic cancer who, following bypass, underwent I-125 implants and 4,000–4,500 cGy postoperative external beam radiotherapy [15]. The median survival was 11 months, but their data did not distinguish T1N0 patients from more advanced patients. Syed et al. [9] treated a group of 18 patients with a similar approach and reported a median survival of 18 months. Mohiuddin et al. [5] reported a median survival of 5.5 months in 13 patients treated with an implant and 50–60 Gy external beam radiation and an increase in median survival to 11.3–12.5 months in patients receiving systemic chemotherapy. However, they failed to analyze their data according to the stage of the disease to demonstrate the impact of treatment on early stage disease.

In our previous series of 98 patients treated with I-125, we demonstrated that four factors significantly affected survival: T stage, N stage, administration of chemotherapy, and more than 30% reduction in the size of implant on follow-up films [7]. The role of chemotherapy in locally advanced carcinoma of the pancreas was first described by Moertel et al. [16], who reported that the combination of 5-FU and radiation produced a significant advantage over radiation alone in the survival of patients with locally advanced tumors (median survival of 10.4 vs 6.3 months, respectively, $P < 0.05$). This result was confirmed in a study by the Gastrointestinal Tumor Study Group, although the 5-FU and radiation were administered in a slightly different regimen [17]. Additional studies have demonstrated that combinations of 5-FU or 5 FU/lomustine (CCNU)/mitomycin C chemotherapy plus radiation have increased median survival from 7 to 14 months [13]. Data in the literature stress the importance of chemotherapy in patients treated with radiation in carcinoma of the pancreas. Our data suggest Pd-103 implantation, when combined with chemotherapy and radiation, provides a viable alternative to I-125 implant for patients with locally advanced, unresectable carcinoma of the pancreas.

Within the constraints of the evaluation methods used in our study, the local control rate is 80%. In general, control of local disease represents a major clinical problem with the existing treatment techniques, including surgery [1,18]. Pain relief occurred in 3–4 weeks after implant. The median duration of pain relief was 6 months. We reported that pain palliation occurred 5–6 weeks after implantation with I-125 and lasted for a median of 6 months [7].

Experience reported in the literature indicates that standard surgical treatment can result in significant morbidity and considerable mortality rates [1,6,18,19]. In a series published by Trede et al. [20], pancreatic leak was the most common complication observed, followed by GI bleeding and fistula formation. Even though the complications with intraoperative brachytherapy are significantly less than with standard surgical procedures, GI bleeding, pancreatic leak, and fistula formation are still considered a not uncommon complication. The complications associated with intraoperative brachytherapy are considered to be a function of the technique and the radioisotope used. Gold-198 was reported to be associated with considerable morbidity, perhaps due to the photon energy of this isotope (0.412 MeV), which delivers excess amounts of radiation to the surrounding normal structures. In our earlier report we described complications with intraoperative brachytherapy using I-125 sources to be significantly less than with gold-198 sources. The treatment-related complications observed in our current series were significantly less than in other published series using intraoperative brachytherapy. We have not encountered any major postoperative complications, such as hemorrhage, fistula

formation, or mortality in the postoperative period, and no serious long-term complications after completion of external beam and chemotherapy. The low morbidity reported in this series may partly be due to a single team performing all the implants and external beam radiation.

CONCLUSIONS

Palladium-103 can be considered as an alternative source to I-125 for interstitial implantation in unresectable carcinoma of the pancreas. Because of its shorter half-life, Pd-103 can be implanted at higher total activities, resulting in subsequent administration of higher dose rates. The surrounding normal tissues, such as the stomach, small bowel, and anastomotic sites, are still spared from radiation damage because the energy spectra of the gamma rays of Pd-103 is similar to that of I-125. This series indicates that the use of Pd-103 in interstitial brachytherapy, combined with chemotherapy and external beam radiation, offers a low morbidity rate and a faster rate of pain palliation, although median survival rates are similar to those observed in patients implanted with I-125. Prospective controlled randomized studies are necessary to determine the superiority of Pd-103 over I-125 in the treatment of unresectable pancreatic cancer.

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